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VIDAS, ARRETT & STEINKRAUS, P.A.
SUITE 400, 6640 SHADY OAK ROAD
EDEN PRAIRIE, MN 55344

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ANDERSON, JAMES D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/682,584	**Applicant(s)** TAS ET AL.	
	Examiner James D. Anderson	**Art Unit** 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007 and 06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12,29,30 and 33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12,29,30 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 2-12, 29-30, AND 33-40 ARE PRESENTED FOR EXAMINATION

Applicants' amendments filed 6/11/2007, 7/16/2007, and 9/6/2007 have been received and entered into the application. Accordingly, claims 2-3, 5, 7, and 29-30 have been amended, claims 1 and 31-32 have been cancelled, and claims 36-40 have been added.

Applicants' arguments, filed 6/11/2007, 7/16/2007, and 9/6/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Unfortunately, upon further consideration of the scope of the claims, the Examiner is herein applying new grounds of rejection under 35 U.S.C. § 112, 1st Paragraph (Written Description) and 35 U.S.C. § 103.

In light of the new rejections being applied against the pending claims, this Office Action is **Non-Final**.

Response to Arguments

Applicant's arguments filed 6/11/2007, 7/16/2007, and 9/6/2007 have been fully considered but they are not persuasive.

With respect to the Beachy *et al.* reference, Applicants' arguments that the reference is not enabling fail to comply with 37 CFR § 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. In this case, Applicants have failed to address the doses that are clearly taught in Beachy *et al.* In this regard, Beachy *et al.* teach that, generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of the invention will range from about 0.0001 to about 100 mg per kilogram of body weight per day. Applicants have not provided any evidence that doses within this range will not induce apoptosis or differentiation in tumor cells as instantly claimed.

While the teachings of Beachy *et al.* are broad, the teachings are reasonably specific with respect to the therapeutic effects that may be achieved. For example, an "effective amount" of the disclosed hedgehog antagonists, with respect to the subject method of treatment, brings about a change in the rate of cell proliferation and/or the state of differentiation of a cell and/or the rate of survival of a cell according to clinically acceptable standards for the disorder to be treated (col. 9, lines 8-14). Applicants are correct that cellular differentiation is said to be "affected" or "altered" or "changed" or "controlled" or "regulated" by the subject method of employing a subject compound of the invention. However, such verbs, while broad, do not render the prior art non-enabled. The fact remains that Applicants have not addressed whether administration of cyclopamine at a dose of 0.0001 to 100 mg per kg body weight to a patient having basal cell carcinoma (or any other tumor for that matter) using the methods of Beachy *et al.* will not result in the claimed induction of apoptosis or cell differentiation.

The hedgehog antagonists of Beachy *et al.* are specifically taught to be useful to cause transformed cells to become post-mitotic or apoptotic (col. 33, lines 21-26). The methods can thus be used as part of a treatment for malignant gliomas, medulloblastomas, neuroectodermal tumors, and ependymomas (col. 33, lines 21-28) as well as in the treatment of cancer, particularly basal cell carcinomas (col. 42, lines 43-49). Beachy *et al.* provide specific teachings with respect to administration routes, formulations, and doses (cols. 43-44). In this regard, it is explicitly taught that the compounds of the invention can be administered in a range from about 0.0001 to about 100 mg per kilogram of body weight per day (col. 44, lines 22-29).

In the present case, the method steps of Beachy *et al.* and the instant claims are indistinguishable. Beachy *et al.* teach methods of "modulating a differentiated state, survival, and/or proliferation of a cell responsive to a hedgehog protein, by contacting the cells with a hedgehog antagonist according to the subject method and as the circumstances may warrant" (col. 29, lines 34-38) and also the treatment of neoplastic or hyperplastic transformations such as may occur in the central nervous system (col. 33, lines 21-23). Such neoplastic transformations reasonably include tumors. In this case, hedgehog antagonists "can be utilized to cause such transformed cells to become either post-mitotic or apoptotic" (*id.* at lines 24-26). Finally, Beachy *et al.* specifically teach the treatment of carcinomas, including basal cell carcinoma (as recited in instant claim 4) (col. 11, lines 9-14; col. 42, lines 43-49).

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-12, 29-30, 33-35, and 37-40 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

1. New Matter

No specific support is seen in the specification as originally filed for the following language:

a) "a compound that binds specifically to a receptor to which cyclopamine binds" in claim 33;

b) "a compound that exerts similarly specific inhibition of Hedgehog/Smoothened signaling as cyclopamine" in claim 37; and

c) "another compound that specifically inhibits Hedgehog/Smoothened signaling" in claims 39 and 40.

2. Inadequate Description

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description"

Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims recite a genus of compounds that is defined only by their biological activity, *i.e.*, a compound that binds specifically to a receptor to which cyclopamine binds (*e.g.*, claim 33), a compound that exerts similarly specific inhibition of Hedgehog/Smoothened signaling as cyclopamine (*e.g.*, claim 37), another compound that specifically inhibits Hedgehog/Smoothened signaling (*e.g.*, claims 39 and 40). There is insufficient written description of the claimed compounds, other than cyclopamine as recited in claim 36. The lack of written description of the instantly claimed genus is further compounded by the fact that the compounds as instantly claimed must specifically bind to a certain receptor (*e.g.*, claim 33) or specifically inhibit Hedgehog/Smoothened signaling (*e.g.*, claim 39). Accordingly, other than cyclopamine, Applicants have not demonstrated possession of the claimed genera of compounds that bind specifically to a receptor to which cyclopamine binds (*e.g.*, claim 33), exert similarly specific inhibition of Hedgehog/Smoothened signaling as cyclopamine (*e.g.*, claim 37), or that specifically inhibit Hedgehog/Smoothened signaling (e.g., claims 39 and 40) as recited in the instant claims.

Aside from cyclopamine as recited in claim 36, Applicants provide no direction as to (a) what subset of compounds out of all possible compounds that exist in the art would have been reasonably expected to have activity instantly claimed and (b) which of those compounds actually *have* the activities instantly claimed without having to execute hit or miss testing practices in order to make such a determination.

Although general techniques such as cellular assays may be known in the art, this fact fails to diminish the amount of experimentation that the skilled artisan would have to undertake to even identify, let alone determine the full scope of, the claimed genera of compounds that bind specifically to a receptor to which cyclopamine binds (*e.g.*, claim 33), exert similarly specific inhibition of Hedgehog/Smoothened signaling as cyclopamine (*e.g.*, claim 37), or that specifically inhibit Hedgehog/Smoothened signaling (*e.g.*, claims 39 and 40), particularly in view of the fact that this genus as a whole is not one that is well-known or well-defined in the art such that the skilled artisan would readily envision those compounds that are within the scope of the claimed genus.

The need for testing amongst varying species of compounds to determine the full scope of the genera of compounds instantly claimed demonstrates that Applicants were not in possession of the full scope of the genera of compounds now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure of cyclopamine, it remains that the specification provides non-limiting exemplification of solely functional genera of agents that may be used within the context of the present invention. With the exception of cyclopamine as defined in the original disclosure and claims, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other agents that may have any of the disclosed functions, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, *e.g.*, *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other agents that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such compounds, and, therefore, did not have written description of the full scope of the genus claimed.

Further, though Applicants have limited the claimed agents to those that perform a particular function, *e.g.*, those that have activities similar to cyclopamine, it remains that Applicants have not appropriately defined the metes and bounds of the genus, even when limited by function (step-plus-function form). As taught in the MPEP at § 2163, step-plus-function claims are not adequately described if "the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a step-plus-function claim limitation," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application fails to meet these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function that would correlate a common structural element or material to performance of the claimed function and that would be readily identifiable to one of skill in the art.

The same reasoning applies equally to the determination of the claimed tumor cells or tumors that "use the Hedgehog/Smoothened signaling for inhibition of apoptosis" (claims 33, 37, and 39) and tumor cells that "use the Hedgehog/Smoothened signaling for inhibition of differentiation" (claim 40). The fact that one of ordinary skill in the art at the time of the invention would need to identify those tumor cells that use the Hedgehog/Smoothened signaling for inhibition of apoptosis or differentiation, with no guidance from Applicants' disclosure, is clear and unequivocal evidence that Applicants were not in possession of the claimed methods of treating tumor cells or patients having tumor cells that use the Hedgehog/Smoothened signaling for inhibition of apoptosis or differentiation, other than basal cell carcinoma, trichoepithelioma, and melanocytic tumors.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2-6, 8-9, 11-12, 29-30, and 33-40 are again rejected under 35 U.S.C. § 102(e)(2) as being anticipated by Beachy *et al.* (U.S. Patent No. 6,432,970 B2; Issued Aug. 13, 2002; Filed Jun. 4, 1998).

The instant claims recite methods for treating tumor cells that use Hedgehog/Smoothened signaling for inhibition of differentiation and apoptosis comprising administering a "sufficient quantity" of cyclopamine to induce differentiation and apoptosis of the tumor cells.

Beachy *et al.* teach methods of inhibiting paracrine and/or autocrine signals produced by a hedgehog protein comprising contacting a cell sensitive to the hedgehog protein with a steroidal alkaloid in a sufficient amount to reduce the sensitivity of the cell to the hedgehog protein (Abstract and col. 4, lines 57-62). The reference thus reasonably anticipates contacting susceptible tumor cells with a steroidal alkaloid that inhibits the bioactivity of hedgehog proteins (col. 7, lines 50-54). Hedgehog proteins are taught to be essential for patterning a variety of structures in animal embryogenesis and play a role in regulating cell proliferation and specifying cell identity in diverse systems in adults (col. 7, lines 8-12). The invention taught in Beachy *et al.* relates to the discovery that signal transduction pathways dependent on hedgehog proteins can be inhibited by compounds which disrupt the cholesterol modification of hedgehog proteins and/or which inhibit the bioactivity of hedgehog proteins (*id.* at lines 50-54). Suitable steroid alkaloids include cyclopamine (Figure 1 and col. 19, lines 35-42). The reference thus reasonably anticipates administering cyclopamine to a cell to inhibit the bioactivity of hedgehog proteins. The methods of Beachy *et al.* can be effective for both human and animal subjects (col. 8, lines

62-63). The reference thus anticipates *in vivo* administration. With respect to an "effective amount" of a compound, which reasonably correlates with the instantly claimed "sufficient quantity", Beachy *et al.* teach that an effective amount of, *e.g.*, a hedgehog antagonist, refers to an amount of the antagonist in a preparation which, when applied as part of a desired dosage regimen brings about, *e.g.*, "a change in the rate of cell proliferation and/or the state of differentiation of a cell and/or rate of survival of a cell" according to clinically acceptable standards for the disorder to be treated (col. 9, lines 8-14). The reference thus reasonably anticipates and encompasses inducing differentiation and apoptosis (rate of survival) by administering a hedgehog antagonist. Similarly, "therapeutically-effective amount" is defined as the amount of a compound which is effective to produce some desired therapeutic effect by inhibiting a hedgehog signaling pathway in at least a sub-population of cells in an animal and thereby blocking the biological consequences of that pathway in the treated cells (col. 45, lines 9-17). This teaching reasonably anticipates inducing differentiation and apoptosis in a cell if the "biological consequence" of hedgehog signaling is inhibition of differentiation and apoptosis. With respect to the treatment of tumors as instantly claimed, Beachy *et al.* contemplate the treatment of carcinomas, including basal cell carcinoma (as recited in instant claim 4) (col. 11, lines 9-14; col. 42, lines 43-49). In this regard, Beachy *et al.* teach that the subject method can be used to induce differentiation of epithelially-derived tissue and can provide a basis for differentiation therapy for the treatment of hyperplastic and/or neoplastic conditions involving epithelial tissue (col. 41, lines 17-24). An exemplary application of the method taught in the reference is a method of "modulating a differentiated state, survival, and/or proliferation of a cell responsive to a hedgehog protein, by contacting the cells with a hedgehog antagonist according to the subject method and as the circumstances may warrant" (col. 29, lines 34-38). The reference thus reasonably anticipates inducing differentiation and apoptosis in tumor cells. In another embodiment, the methods of Beachy *et al.* can be used in the treatment of neoplastic or hyperplastic transformations such as may occur in the central nervous system (col. 33, lines 21-23). In this case, hedgehog antagonists "can be utilized to cause such transformed cells to become either post-mitotic or apoptotic" (*id.* at lines 24-26). Such neoplastic transformations reasonably include tumors such as malignant gliomas, medulloblastomas, neuroectodermal tumors, and ependymomas (*id.* at lines 26-29). Pharmaceutical compositions wherein the hedgehog antagonists are formulated for administration with biologically acceptable mediums such as water, buffered saline, polyols or suitable mixtures are taught at column 42, lines 57-62). This teaching anticipates instant claims 5-6. Administration routes include oral, parenteral, topical and rectal (col. 43, lines 26-33). Transdermal patches and topical creams and ointments as recited in claim 11-12 are taught at column 48, lines 62-67 and column 49, lines 8-16. Dosage levels vary so as to achieve the desired therapeutic response for a particular patient, composition and mode of administration (col. 43, line 64 to col. 44, line 2). Generally, for intravenous or subcutaneous administration, the dose of the compounds ranges from 0.0001 to 100 mg per kilogram of body weight per day (col. 44, lines 26-29).

The reference thus clearly anticipates administering a steroid alkaloid such as cyclopamine to tumor cells, thereby inducing differentiation and apoptosis.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-6, 8-9, 11-12, 29-30, and 33-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamb *et al.* (WO 00/74706; Published Dec. 14, 2000; Filed June 5, 2000) (prior art of record) in view of Talpale *et al.* (Nature, 2000, vol. 406, pages 1005-1009) (prior art of record) and Oro *et al.* (Science, 1997, vol. 276, pages 817-821) (prior art of record).

The instant claims relate to treating tumor cells or patients having tumors, wherein the tumor cells use the Hedgehog/Smoothened signaling for inhibition of apoptosis or differentiation.

Lamb *et al.* teach methods of using inhibitors of a Hedgehog signaling, or inhibitors of a pathway that is a target of the Hedgehog signaling pathway, for the treatment of epithelial cell hyperplasia, fibrosis of tissue, inflammation, cancer, or an immune disorder (Abstract; page 2, lines 14-18). Cyclopamine, as instantly claimed, is exemplified as a preferred inhibitor (page 3, line 11). Hedgehog signaling is disclosed as mediated by two transmembrane proteins, *Patched* and *Smoothened* (page 8, lines 12-15). *Smoothened* is a constitutive activator of Hedgehog target genes, whose activity is normally repressed by *Patched*, and this repression is relieved by Hedgehog binding to *Patched* (*id.* at lines 16-17). The invention of Lamb *et al.* also contemplates that mutations that result in loss of normal function of the regulators of the Hedgehog signaling pathway or regulators of the a pathway which is a target of the Hedgehog signaling pathway in human disease states can be inhibited by Hedgehog antagonists in such disease states (page 12, lines 1-10). Mutations of Hedgehog can lead to the human autosomal disorder Nevoid basal cell carcinoma syndrome (NBCCS), which is characterized by developmental abnormalities and a high predisposition for various forms of cancer mainly the very common basal cell carcinoma (BCC) (paragraph bridging pages 28-29). The treatment of cancer, particularly in diseases involving the conversion of epithelial cells to cancer is disclosed, as is the treatment of adenocarcinomas such as small cell lung cancer, and cancer of the kidney, uterus, prostate, bladder, ovary, colon, and breast (page 32, lines 11-14). Topical, parenteral, intramuscular, intravenous, and intraperitoneal administration of the disclosed compounds is taught at page 37, lines 15-25. Dosages and formulations are disclosed at pages 38-40. The reference thus obviates the limitations of claims 5-12.

Talpale *et al.* teach that basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors are associated with mutations that activate the proto-oncogene *Smoothened* (*SMO*) or that inactivate the tumor suppressor *Patched* (*PTCH*) (Abstract). *Smoothened* and *Patched* mediate the cellular response to the Hedgehog secreted protein signal, and oncogenic mutations affecting these proteins cause excessive activity of the Hedgehog response pathway. The authors demonstrate that the plant-derived teratogen cyclopamine, which inhibits the

Hedgehog response, is a potential "mechanism-based" therapeutic agent for the treatment of tumors such as basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors that are associated with mutations that activate the proto-oncogene *Smoothened* or that inactivate the tumor suppressor *Patched* (Abstract). In this regard, the authors show that cyclopamine blocks activation of the Hedgehog response pathway and abnormal cell growth associated with both types of oncogenic mutations (Abstract and Figures 1-4). The results presented by Talpale *et al.* indicate that cyclopamine inhibits the Sonic hedgehog (Shh) pathway by antagonizing *Smoothened* and that the activation of the Hedgehog response pathway by either type of oncogenic mutation (*i.e.*, mutations that activate the proto-oncogene *Smoothened* or that inactivate the tumor suppressor *Patched*) is blocked by cyclopamine (page 1008; Figure 4c). The authors conclude that cyclopamine could be used to reverse activation of the Shh response pathway for therapeutic purposes.

Oro *et al.* is provided as further evidence that basal cell carcinoma (as recited in instant claim 4) over expresses Sonic hedgehog and that mutations in the tumor suppressor gene *Patched* are found in human patients with basal cell nevus syndrome, a disease causing developmental defects and tumors, including basal cell carcinomas (Abstract). The data in Oro *et al.* "suggest that *SHH* [Sonic hedgehog] may have a role in human tumorigenesis" (Abstract).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art suggests and motivates the use of inhibitors of Hedgehog signaling, or inhibitors of a pathway that is a target of the Hedgehog signaling pathway, for the treatment of epithelial cell hyperplasia, fibrosis of tissue, inflammation, cancer, or an immune disorder (Lamb *et al.*). The prior art further teaches that Hedgehog/Smoothened is implicated in various human tumors, including basal cell carcinoma (Talpale *et al.* and Oro *et al.*). It is also taught in the prior art that cyclopamine inhibits the Sonic hedgehog (Shh) pathway by antagonizing *Smoothened* and that the activation of the Hedgehog response pathway by either type of oncogenic mutation *mutation* (*i.e.,* mutations that activate the proto-oncogene Smoothened or that inactivate the tumor suppressor *Patched*) is blocked by cyclopamine. Finally the prior art suggests that cyclopamine could be used to reverse activation of the Shh response pathway for therapeutic purposes (Talpale *et al.*).

Though Lamb *et al.* do not expressly teach the induction of apoptosis or differentiation as a result of the administration of the disclosed compounds to either the subject or cell cultures, the administration of the same compound(s) as claimed (*e.g.*, cyclopamine) to the same host (*i.e.*, a human having basal cell carcinoma or basal cell carcinoma tumor cells) as claimed is considered to necessarily have the claimed effect of inducing differentiation or apoptosis on the subject or cell being treated, whether expressly recognized by Lamb *et al.* or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP § 2112.

Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the fact that such a property may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one or ordinary skill in the art at the time the invention was made to use cyclopamine to treat tumors in which Hedgehog/Smoothened is implicated as suggested and motivated by Lamb *et al.* and Talpale *et al.* In this regard, the Examiner makes the following findings of fact:

(i) at the time of the invention, there was a recognized need in the art to solve the problem of developing antitumor agents that are specific to certain signaling pathways such as Hedgehog/Smoothened;

(ii) there were a finite number of predictable solutions for treating tumors wherein Hedgehog/Smoothened is implicated (*e.g.*, treating such tumors with an inhibitor of Hedgehog signaling; and

(iii) one of ordinary skill in the art could have pursued the known options with a reasonable expectation of success (*e.g.*, administering cyclopamine, which inhibits the Hedgehog response, to tumors such as basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors that are associated with mutations that activate the proto-oncogene *Smoothened* or that inactivate the tumor suppressor *Patched*).

The rationale to support the conclusion that the instant claims would have been obvious is that a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense.

In the present case, it is clear from the prior art that Hedgehog/Smoothened signaling was implicated in numerous tumor types, especially basal cell carcinomas. It is suggested in the prior art that inhibitors of Hedgehog signaling, or inhibitors of a pathway that is a target of the Hedgehog signaling pathway (*e.g.*, cyclopamine), could be used for the treatment of epithelial cell hyperplasia, fibrosis of tissue, inflammation, cancer, or immune disorders. Cyclopamine was known in the art to inhibit the Sonic hedgehog pathway by antagonizing *Smoothened* and that the activation of the Hedgehog response pathway by mutations that activate the proto-oncogene *Smoothened* or that inactivate the tumor suppressor *Patched* is blocked by cyclopamine. As such, one skilled in the art would have been imbued with at least a reasonable expectation that administration of cyclopamine to tumors wherein Hedgehog signaling is implicated would block activation of Hedgehog signaling and thus treat such tumors. Applicants' discovery that higher doses of cyclopamine topically administered to treat basal cell carcinoma results in apoptosis and/or differentiation does not render any less obvious the use of cyclopamine to treat basal cell carcinomas. There is no evidence of record that the doses suggested in Lamb *et al.* would not result in the claimed effects when administered to a patient having a tumor that uses Hedgehog/Smoothened signaling for inhibition of apoptosis (*e.g.*, basal cell carcinoma).

Claims 7 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Beachy *et al.* (U.S. Patent No. 6,432,970 B2; Issued Aug. 13, 2002; Filed Jun. 4, 1998) as applied to claims 2-6, 8-9, 11-12, 29-30, and 33-40 above.

Instant claim 7 recites liposomal forms of the claimed compounds. Instant claim 10 recites a controlled release form of the claimed compounds.

Beachy *et al.* disclose as discussed *supra*. In summary, the reference teaches pharmaceutical compositions and formulations of steroid alkaloids suitable for administering to humans.

In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed pharmaceutical dosage forms would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The skilled artisan would have been highly motivated to optimize and modify the dosage forms disclosed in Beachy *et al.* Liposomal and controlled release formulations are well known in the art for the administration of therapeutic agents. As such, it is not unobvious to administer a therapeutic drug in such formulations. Beachy *et al.* disclose numerous pharmaceutically-acceptable carriers that may be used to administer the disclosed steroid alkaloids (col. 45, lines 26-51). As such, it would have been obvious that other carriers, including liposomes and controlled release carriers, could also be used to effectively administer the compounds disclosed therein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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James D. Anderson
Patent Examiner
AU 1614

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11/18/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER